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References and Notes

(1) W. Hieber and J. Gruber, *Z. Anorg. Allg. Chem.*, **296**, 91 (1958).
(2) C. H. Wei and L. F. Dahl, *Inorg. Chem.*, **4**, 1 (1965).
(3) N. S. Nametkin, V. D. Tyurin, and M. A. Kukina, *J. Organomet. Chem.*, **149**, 355 (1978).
(4) N. S. Nametkin, V. D. Tyurin, O. V. Kuz'min, A. I. Nekhaev, and M. Mavlonov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2143 (1976).
(5) (a) D. Seyferth, *Adv. Organomet. Chem.*, **14**, 97 (1976); (b) D. Seyferth and J. S. Merola, *J. Am. Chem. Soc.*, **100**, 6783 (1978).
(6) R. B. King, *J. Am. Chem. Soc.*, **84**, 2460 (1962).
(7) L. F. Dahl and C. H. Wei, *Inorg. Chem.*, **2**, 328 (1963).
(8) W. L. Jolly, "The Synthesis and Characterization of Inorganic Compounds", Prentice-Hall, Englewood Cliffs, N.J., 1970, p 476.
(9) H. Reihlen, A. Gruhl, and G. Hessling, *Justus Liebigs Ann. Chem.*, **472** 268 (1929).
(10) E. W. Abel and B. C. Crosse, *Organomet. Chem. Rev.*, **2**, 443 (1967).
(11) H. Vahrenkamp, *Angew Chem.*, **87**, 363 (1975).

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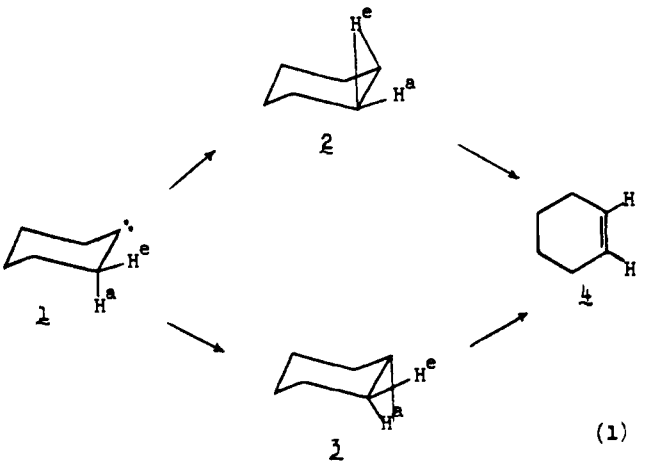
The Case for Stereoelectronic Axial Migration of Hydrogen in Nonrigid Cyclohexylidenes in Chair Conformation

Sir:

The stereochemistry of 1,2 rearrangements in carbenes is an important mechanistic question.[1] Brexan-5-ylidene, a rigid singlet cyclohexylidene in strained boat conformation, is presumed to undergo rearrangement of its exo α hydrogen 138 times faster than its endo hydrogen because migration is greatly favored for hydrogen which is nearly parallel to the vacant p orbital of the carbene.[1f] Subsequently, rearrangements of α-methine hydrogen and of α-phenyl occurring 1.46 and 0.20 times as extensively in *cis*- than in *trans*-4-*tert*-butyl-2-phenylcyclohexylidenes were interpreted to indicate that such migrations occur preferentially by axial processes.[1j] Recently, the migratory ratio, H(axial)/H(equatorial), of hydrogen from the 6 positions of 4-*tert*-butyl-2,2-dimethylcyclohexylidene was found to be 1.50.[1k] This result was theorized, however, to involve little stereoelectronic control during rearrangement. In conjunction with MINDO/3 or MNDO

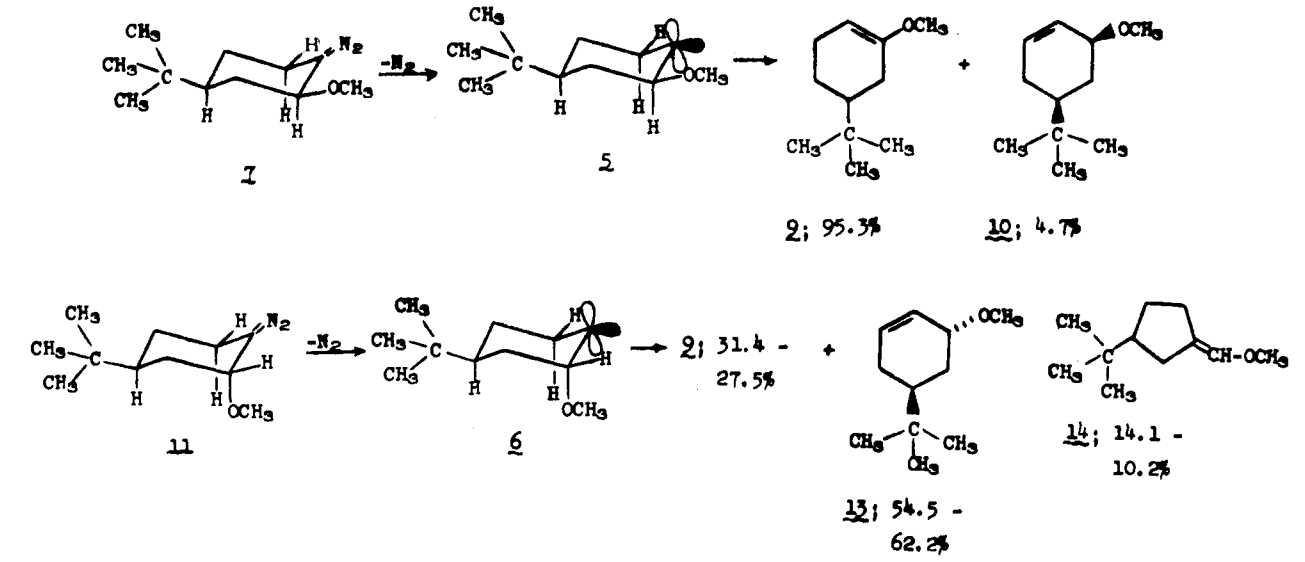


calculations,[11] it was then suggested that the activation energy for rearrangement of a nonrigid, chair-like cyclohexylidene (**1**) in which H^e migrates toward the empty carbenic orbital with realignment of H^a as in **2** is essentially equal to that to **3** or to alternate transition states.[11]

A study is now reported of the carbenic rearrangements of 4-*tert*-butyl-*cis*-2-methoxycyclohexylidene (**5**) and 4-*tert*-butyl-*trans*-2-methoxycyclohexylidene (**6**). These systems indicate clearly the significance of axial stereochemical preferences for migration in these conformationally restricted cyclohexylidenes. The results also (1) raise the question that the recent calculations for rearrangement of cyclohexylidene may be overextended[11] and (2) allow definition of factors in substituted flexible cyclohexylidenes which lead to rearrangement with apparent minimal stereoelectronic control.[1k,l]

Thus 1-diazo-2-methoxy-*cis*-4-*tert*-butylcyclohexane (**7**), generated in situ from sodium 2-methoxy-*cis*-4-*tert*-butylcyclohexanone *p*-tosylhydrazonate (**8**),[2a-c] decomposes in diglyme[2c] at 190 °C to 5-*tert*-butyl-1-methoxycyclohexene (**9**, 95.3%) and 5-*tert*-butyl-*cis*-3-methoxycyclohexene (**10**, 4.7%) (Scheme I), products of hydrogen migration from C-2 and C-6, respectively.[2d] Similar results are obtained by pyrolysis of dry **8** at 190 °C. In contrast, thermolysis of 1-diazo-2-methoxy-*trans*-4-*tert*-butylcyclohexane (**11**), as derived from sodium 2-methoxy-*trans*-4-*tert*-butylcyclohexanone *p*-tosylhydrazonate (**12**)[2a-c] at 190 °C in diglyme,[2c] gives **9** (31.4%) and 5-*tert*-butyl-*trans*-3-methoxycyclohexene (**13**, 54.5%) by hydrogen migration and 3-*tert*-butyl(methoxymethylene)cyclopentane (**14**, 14.1%) by ring contraction.[2d]

Scheme I



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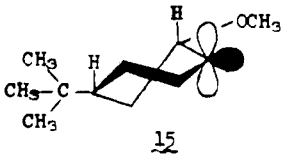
Dry **12** pyrolyzes analogously at 190 °C to **9** (27.5%), **13** (62.2%), and **14** (10.2%). Methoxy migration does not occur in rearrangement of **5** or **6.**

The difference in product composition from thermolyses of **7** and **11** is striking. First, the ratio of **9** from **7** to **9** from **11** is ~3.5:1. More impressive is the occurrence of **13** as the major product from **11;** 13 times more hydrogen migration occurs from C-6 in **6** to give **13** than from C-6 in **5** to **10** even though the repulsive 1,3-diaxial interactions in **13** are greater than in **10.** That **13** is formed in greater percentage than **9** is significant since the methoxy group enhances carbenic migration of other groups from the carbon atom to which it is attached.[3] Finally, and of greatest interest, is that the product proportions from **7** and **11** lead to apparent migratory ratios of H^a from C-2 in **5** to H^e from C-2 in **6** ranging from 35–46:1.[4-6]

These results may be rationalized as follows. In **5,** on the basis of equatorial preference of its *tert*-butyl group and (nearly) sp^2 hybridization of the carbenic center, the methine hydrogen is presumably nearly perpendicular to the filled, nonbonding orbital at C-1, whereas, in **6,** the methine hydrogen is conformationally restricted to an antiplanar orientation[1g] as modified by the diaxial interactions of its methoxy group. In **6,** hydrogen migrates from C-6 (apparently preferentially from an axial position) rather than from the equatorial position at C-2 in spite of extra stabilization of positive charge and relief of 1,3-diaxial interactions from the methoxy group. That little rearrangement of hydrogen from C-6 occurs in **5** and that ring contraction is observed in **6** is consistent with the effect in which the methoxy group enhances migration of other substituents.[3]

The present observations thus imply that, for cyclohexylidenes such as **5** and **6** in chair-like conformation, transition state **2** is more difficult to achieve than **3.** A possible reason for this is that hydrogen bridging is not highly developed in such rearrangements and the transition states reflect much of the structure of the reactant, **1.** Thus the interaction at the vacant orbital of the carbenic center is greater with α-axial than with α-equatorial hydrogen. Such effects may be quite large in systems as in **5** in which hydrogen has marked abilities to migrate because of electronic factors.[7]

A remaining significant and as yet unsolvable question is whether **9** is produced as a minor product from **6** by (1) equatorial rearrangement as for **2** and/or (2) conversion to twist-boat or even inverted chair forms and hydrogen migration from pseudoaxial (as in **15**) or axial positions. Rearrangement



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of equatorial hydrogen in **2** allows preservation of the chair-like structure of the ring system and effective relief of 1,3-diaxial interactions at carbon from which hydrogen migrates. On the other hand, it is unlikely that **6** is conformationally fixed at 190 °C and, at a hypothetical concentration of **15** as small as 2%, migration of α-methine hydrogen (pseudoaxial) ~15 times faster than α-methylene hydrogen will account for **9.** What is clear, however, is that, in cyclohexylidenes in which there are extensive diaxial repulsions, either of the above mechanisms will account for the nearly competitive migration of equatorial and axial α hydrogen.[1k,l]

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References and Notes

(1) (a) J. W. Powell and H. C. Whiting, *Tetrahedron,* **12,** 168 (1961); (b) R. Hoffman, G. D. Zeiss, and G. W. Van Dine, *J. Am. Chem. Soc.,* **90,** 1485 (1968); (c) N. Bodor and M. J. S. Dewar, *ibid.,* **94,** 9103 (1972); (d) O. S. Tee and K. Yates, *ibid.,* **94,** 3074 (1972); (e) H. E. Zimmerman, *Acc. Chem. Res.,* **5,** 393 (1972); (f) J. A. Altman, I. G. Csizmadia, and K. Yates, *ibid.,* **96,** 4196 (1974); (g) A. Nickon, F.-C. Huang, R. Weglein, K. Matsuo, and H. Yagi, *ibid.,* **96,** 5264 (1974); (h) J. A. Altmann, I. G. Csizmadia, and K. Yates, *ibid.,* **97,** 5217 (1975); (i) E. P. Kyba and C. W. Hudson, *ibid.,* **98,** 5696 (1976); (j) J. A. Altmann, O. S. Tee, and K. Yates, *ibid.,* **98,** 7132 (1976); (k) L. Seghers and H. Shechter, *Tetrahedron Lett.,* 1943 (1976); (l) E. P. Kyba and C. W. Hudson, *J. Org. Chem.,* **42,** 1935 (1977); (m) P. K. Freeman, T. A. Hardy, J. R. Balyeat, and L. D. Westcott, *ibid.,* **42,** 3356 (1977); (n) E. P. Kyba and A. M. John, *J. Am. Chem. Soc.,* **99,** 8329 (1977); (o) E. P. Kyba, *ibid.,* **99,** 8330 (1977).

(2) (a) 2-Methoxy-*cis*-4-*tert*-butylcyclohexanone and 2-methoxy-*trans*-4-*tert*-butylcyclohexanone were prepared by prior methods[2b] and converted to their *p*-tosylhydrazones under conditions such that stereochemical integrity was preserved. (b) Private communication, W. Chodkiewicz, Laboratoire de Recherches de Chimie Organique, Paris, France. (c) The *p*-tosylhydrazones were decomposed homogeneously in excess (up to 2.6 equiv) sodium hydride or sodium methoxide. The decompositions in solution or dry were satisfactorily reproducible throughout. (d) Products **10** and **13** were identified by GLC comparison with authentic samples; **9** (stereochemistry unknown) and **14** were hydrolyzed to 3-*tert*-butylcyclohexanone and 3-*tert*-butylcyclopentanecarboxaldehyde, respectively.

(3) W. Kirmse and M. Buschoff, *Chem. Ber.,* **100,** 1491 (1967); K. A. Gould, Ph.D. Dissertation, The Ohio State University, 1975.

(4) Calculated by multiplying the ratio of **9:10** from **5** by the ratio of **13:9** from **6** on the basis that the products formed are related to the rate constants, k_H, for migration of the indicated H by

$$\frac{k_H^a(\text{C-2 in } \mathbf{5})}{k_H^e(\text{C-2 in } \mathbf{6})} = \frac{k_H^a(\text{C-2 in } \mathbf{5})}{k_H^{a+e}(\text{C-6 in } \mathbf{5})} \times \frac{k_H^{a+e}(\text{C-6 in } \mathbf{6})}{k_H^e(\text{C-2 in } \mathbf{6})}$$

and assuming that the overall rate constants for migration of H^a and H^e from C-6 in **5** and **6** are essentially identical because 2-OCH_3 has small transannular steric (*A* value = 0.5–0.7 kcal/mol) and electronic effects.

(5) (a) On the basis that (1) H^a at C-6 in **6** is repelled by 2-$OCH_3{}^a$ at C-2, (2) the transition states for rearrangement of **6** (and **5**) are close to reactant, and (3) movement of H^a on C-6 into alignment with the empty p orbital at C-1 is retarded by 2-$OCH_3{}^a$, conversion to **13** as in **3** may actually be depressed, and the calculated migratory ratio may be smaller than in reality. (b) Steric release of H^a from C-6 in **6** resulting in an enhanced rate of formation of **13** is anticipated to be minor because 2-OCH_3 is small and the reaction transition state is predicted to resemble **6.** Further, such steric releases in **6** would also be expected to result in minor acceleration of formation of **9.** Thus accelerated conversions of **6** to **9** and **13** would be significantly cancelled in their net effects. (c) If it is assumed that the percentage of **9** from **6** has been specifically lowered totally by the conversion to **14,** the migratory ratios still calculate to be 24–34:1.

(6) On the assumption that the rearrangements have identical probability factors, these migratory ratios correspond to activation energy differences of ~3.3–3.5 kcal/mol at 190 °C.

(7) Migration of H^a from C-2 in **5** may be enhanced because 2-$OCH_3{}^e$ is nearly perpendicular to the vacant p orbital at C-1 and thus more capable of inductive electron donation than is 2-$OCH_3{}^a$ (as in **6**) to hydrogen rearrangement.

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Stereochemical Course of Glycerol Kinase, Pyruvate Kinase, and Hexokinase: Phosphoryl Transfer from Chiral [$\gamma(S)$-^{16}O,^{17}O,^{18}O]ATP

Sir:

We recently reported the stereoselective synthesis of a chiral [^{16}O,^{17}O,^{18}O]phosphate monoester and the independent determination of the absolute configuration at phosphorus in this molecule.[1,2] We now show that the synthetic method can be used to generate [γ-^{16}O,^{17}O,^{18}O]ATP of one configuration at the γ-phosphorus and that this material, when used as a substrate in the glycerol kinase reaction, results in the formation of isotopically labeled *sn*-glycerol 3-phosphate having the opposite configuration at phosphorus. Since we have earlier demonstrated that glycerol kinase, pyruvate kinase, and hexokinase have an identical stereochemical consequence at phosphorus,[3] we may conclude that *the transformations catalyzed by each of these enzymes proceed with inversion of the configuration at phosphorus.*

The synthesis of [$\gamma(S)$-^{16}O,^{17}O,^{18}O]ATP is outlined in Scheme I, and is an adaption of our earlier approach to chiral [^{16}O,^{17}O,^{18}O]phosphate monoesters.[1] Reaction of [^{17}O]-

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